Telling the liver (not) to make bile acids: a new voice from the gut?

The maintenance of adequate amounts of bile acids in the liver, biliary tract, and intestine requires a finely tuned control of their synthesis. A paper in this issue of *Cell Metabolism* by Inagaki et al. (2005) indicates that sensing of the levels of bile acids in the intestine may trigger the secretion of a hormone which regulates bile acid production in the liver.

Bile acids, made from cholesterol in the liver, are detergent molecules which are secreted as conjugates into hepatic bile, stored in the gallbladder, and propelled into the duodenum as part of the integrated physiological response to a meal. After contributing to the absorption of fat, cholesterol, and fat-soluble vitamins in the upper small intestine, most bile acids are actively reabsorbed in the terminal ileum and returned to the liver via the portal vein. The nonabsorbed fraction is excreted in the feces and needs to be replaced by de novo synthesis in order to maintain an intact bile acid pool in the enterohepatic circulation. This flux of bile acids can be influenced by several factors, such as gallbladder function and intestinal motility, but also by changes in diet and the intestinal microflora which may modify the individual bile acid molecules. Since stimulation of bile acid synthesis elicits favorable compensatory responses, including mobilization of cholesterol by the liver, thereby decreasing the plasma levels of atherogenic lipoproteins, the notion of manipulating the normal enterohepatic circulation for therapy has been revitalized (Angelin et al., 1999).

The concept of bile circulation dates back to the seventeenth century, shortly after Harvey described the paradigm for blood. Following on from key results obtained using animals in the late-nineteenth century (Reuben, 2005), the dynamics of the enterohepatic circulation have been under constant investigation. However, despite the molecular elucidation of important gate-keeping structures (Figure 1) in the last few years, our understanding of how the body regulates the major pathway of cholesterol degradation is still incomplete. Bile acids are believed to exert end-product feedback inhibition of their own synthesis at the completion of their cycle. The uniqueness of this regulation is obvious, since the end-product has to pass through a number of organs before reaching its final

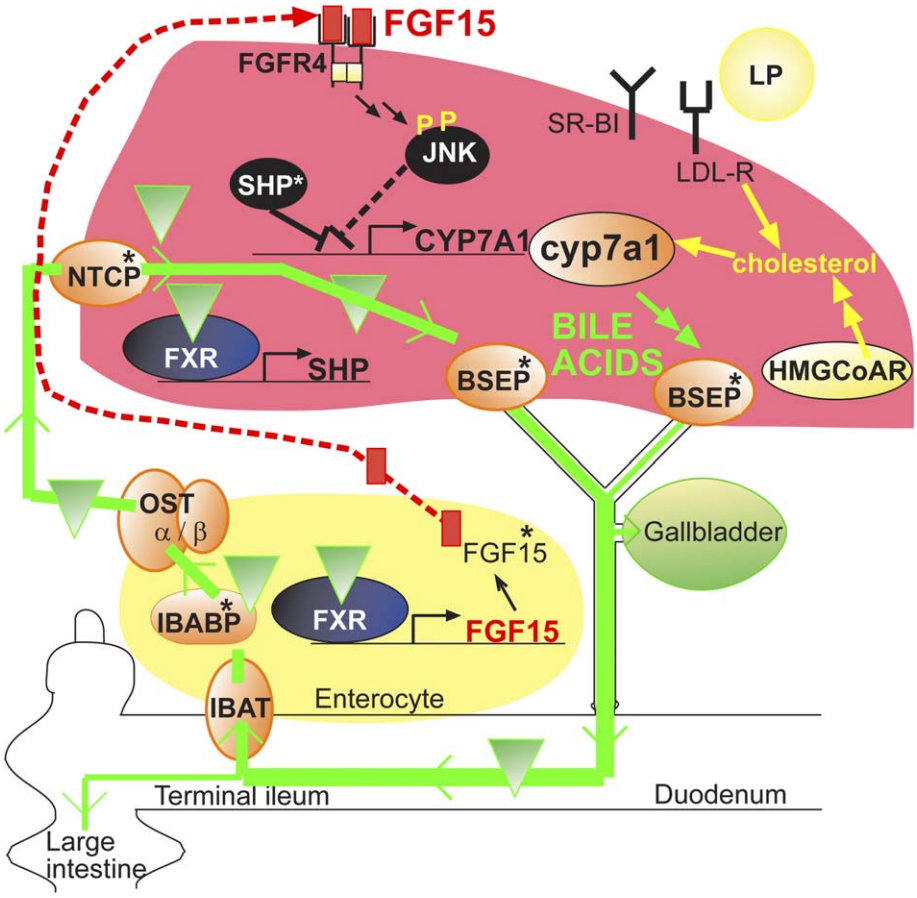

Figure 1. Enterohepatic circulation of bile acids

Cholesterol, derived from circulating lipoproteins or from de novo synthesis in the liver, is converted to bile acids through chemical modifications initiated by 7α-hydroxylation. After conjugation to taurine or glycine, bile acids are actively secreted from the hepatocyte, together with free cholesterol and phospholipids, and are retained in the gallbladder during fasting. In response to a meal, cholecystokinin is released from the gut, resulting in the release of concentrated bile to the duodenum, where the detergent bile acids promote the absorption of dietary fat. Passive uptake of some bile acids occurs along the small intestine, but the major fraction is taken up by active transport in the terminal ileum. Bile acids are theniu transported in the portal vein back to the liver, where they are actively taken up in hepatocytes and resecreted into bile, thereby completing their enterohepatic circulation. The amount of bile acids lost in the feces is compensated for by de novo synthesis of bile acids by the liver, resulting in the maintenance of an intact pool of bile acids in the body. The sensing of the amount of circulating bile acids can be achieved by the interaction of returning bile acids in the hepatocyte but may also be the result of bile-acid-controlled release of FGF15 from the enterocyte.

Abbreviations: BSEP, bile salt export pump; CYP7A1, cholesterol 7α hydroxylase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; HMG CoAR, 3-hydroxy-3-methylglutaryl CoA reductase; IBABP, ileal bile acid binding protein; IBAT, ileal bile acid transporter; JNK, c-Jun WH_2-terminal kinases; LDL-R, low-density lipoprotein receptor; LP, lipoproteins; NTCP, sodium taurocholate cotransporting polypeptide; OST, organic solute transporter; SHP, short heterodimer partner; * indicates structures directly regulated by FXR.

Figure created by Thomas Lundåsen, Center for Nutrition and Toxicology, Department of Biosciences at Novum, Sweden.

point of metabolic control in this pathway. The proposal of a new intestinal signaling mechanism which may contribute to the maintenance of an adequate bile acid pool by Inagaki et al. (2005) provides a new thrust to the field.

The major pathway of bile acid biosynthesis is controlled by the activity of the microsomal enzyme cholesterol 7α hydroxylase (CYP7A1; Chiang, 2004). The transcriptional control of this gene is complex and still not fully understood. Bile acids activate the nuclear receptor farnesoid X receptor (FXR) in the liver, which indirectly results in the repression of *Cyp7a1* transcription by the orphan nuclear receptor small heterodimer partner (SHP) partnered to the liver receptor homolog-1 (LRH-1). FXR/SHP-independent regulators of CYP7A1 expression, such as PPAR-α and pregnane X receptor have also been documented. In addition, in rodents—but not in humans—the transcription of *Cyp7a1* is stimulated by cholesterol metabolites via the liver X receptor (LXR). Recently, the fibroblast growth factor FGF19, which is under the control of FXR, through its interaction with its receptor FGFR4, has been shown to downregulate CYP7A1 (Holt et al., 2003, Yu et al., 2000, 2005). Besides *Cyp7a1*, many of the genes modulating the dynamics of enterohepatic circulation of bile acids are also FXR regulated, indicating the importance of controlling their activity in response to bile acid concentrations (Figure 1). Until now, some of the previous observations in the field had been difficult to reconcile. For instance, blocking the intestinal flow of bile acids by ligation of the bile duct increases CYP7A1 expression and activity, despite resulting in high concentrations of bile acids in the liver (Gustafsson, 1978), while reinfusion of bile acids into the intestine rapidly downregulates CYP7A1 expression, an effect that is not seen upon intravenous or even portal administration of bile acids (Pandak et al., 1991).

Inagaki et al. (2005) now show that the mouse ortholog of FGF19, FGF15, is expressed in the small intestine, but not in the liver, and that it is regulated by FXR (Li et al., 2005). Infusion of FGF15 results in repression of *Cyp7a1* and downregulation of CYP7A1 activity and fecal bile acid excretion through a mechanism involving FGFR4 and, at least partly, SHP. The authors propose that the synthesis and release of FGF15 in the small intestine functions as an enterohepatic signal which senses bile acid uptake and regulates hepatic bile acid synthesis in an "endocrine" loop. This hypothesis may be helpful in explaining some of the contradictory observations on the regulation of bile acid synthesis mentioned above.

Further studies will have to elucidate the detailed mechanisms of how FGF15/19 and FGFR4 exert their effect on CYP7A1 expression and activity and how this potential pathway may overlap with bile acid/FXR regulation. It will also be important to characterize the cells expressing FGFs and the details of their secretion. The development of an assay to measure circulating FGFs will be crucial in understanding how FGFs may act as intestinal hormones and whether this phenomenon is relevant in humans.

The possible presence of a gut-liver signaling pathway may additionally help in the understanding of how distinct and rapid diurnal variation in bile acid synthesis is controlled. Recent studies in humans have established that bile acid production displays two distinct peaks during daytime, with variations unrelated to feeding (Gälman et al., 2005). It is probable that this pattern is induced by a "clock function" from the hypothalamus and turned off by postprandial inflow of bile acids in the portal vein or, alternatively, by an inflow of gut-derived FGF. The potential role of intestinal signaling to the liver by FGF (and other molecules) has added a new promising dimension to the ancient concept of enterohepatic circulation of bile.

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